Theoretical Study of Binding of Tetramethylammonium Ion with Aromatics

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ABSTRACT: *Ab initio* computations including correlation have been performed in a comparative study of complexes of tetramethylammonium (TMA) with benzene, pyrrole, pyridine, and imidazole, using polarized Gaussian basis sets of different accuracies. With the best basis (optimized on molecular polarizabilities), the BSSE-corrected binding energies in the most stable complexes of these four ligands are 9.1, 10.7, 13.3, and 16.3 kcal/mol, respectively, with benzene and pyrrole binding in a plane perpendicular to the TMA axis, and pyridine and imidazole inserting their nitrogen lone pair essentially along the TMA axis. The characteristics of secondary sites of binding of benzene are also determined and the overall results are discussed in connection with the possible role of aromatic amino acids in proteins. © 1997 John Wiley & Sons, Inc. *J Comput Chem* **18**: 2012–2022, 1997

Keywords: tetramethylammonium (binding to aromatics); cation–π interaction; benzene; pyrrole; imidazole; pyridine; phenylalanine, tyrosine, tryptophan

Introduction

Numerous early experimental observations[1–4] have established that quaternary ammonium ions interact favorably with aromatic compounds rich in π electrons. The probable importance of such interactions in biological recognition processes has been emphasized by Dougherty et al.[5] on the basis of a number of observations by their group and others.[6–9] Recently, X-ray analysis of the structure of the enzyme acetylcholine esterase[10–12] showed that a ''gorge'' leading to the site of bonding of the acetylcholine molecule is lined by 14 aromatic side-chains, suggesting that these residues could form a succession of loci of favorable interaction with the onium head of the molecule, helping it to ''slide'' down the gorge. Theoretical calculations[13, 14] using molecular modeling have been performed on the interaction of

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acetylcholine with a model of the gorge built with X-ray coordinates of 23 amino acids lining its walls. These calculations showed that, indeed, the molecule encountered a series of local sites disposed from top to bottom of the gorge in successive regions of increasing interaction, which culminated in the region of the ''active site,'' with the aromatic residues intervening in various ways in all the energy minima detected.

Further theoretical rationalization of the types of interactions involved in such ''cation–π'' binding was hampered by the absence of quantum mechanical calculations of high quality, allowing, for example: comparison of the intrinsic affinities of different aromatics for a given onium cation; an understanding of the underlying contributions to the binding; knowledge of the preferred structure of the best complexes; degree of their conformational lability; and so forth. In view of obtaining such information, we have performed *ab initio* theoretical computations, including correlation, of the binding properties of a series of aromatics to the tetramethylammonium ion $N(CH_3)_4^+$ (TMA). The aromatic systems considered in this article are four related compounds containing six π electrons, namely benzene and three nitrogen-containing cycles, pyrrole, imidazole, and pyridine (Fig 1a, b, c, and d, respectively). Benzene and imidazole are the cycles of the amino acids phenylalanine and unprotonated histidine, and pyrrole is the pentacycle of tryptophan. Although benzene is generally viewed as the prototype of cation–π interactions,[1,15–17] an exploration of the modifications of its binding properties upon heteroatomic substitution and distortion of its π system should improve our understanding of this type of interaction in proteins and elsewhere and hopefully help to conceive more efficient host molecules for various onium guest cations.

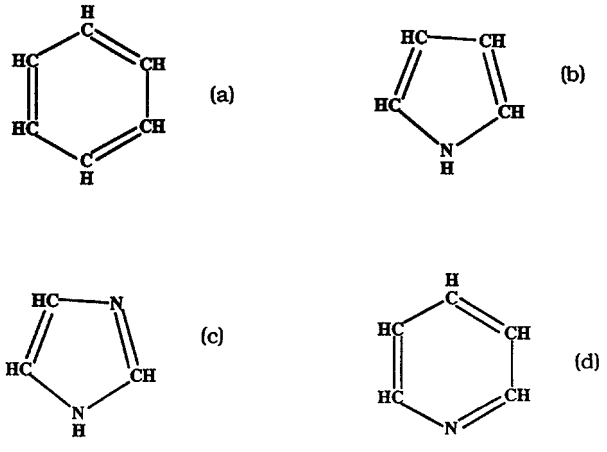

FIGURE 1. The four π systems considered: (a) benzene; (b) pyrrole; (c) imidazole; (d) pyridine.

Computational Details

The complexes considered have been treated using the supermolecule approach where the two entities, A and B, in the interaction are considered as a single system, treating all the electrons of the ensemble AB in the field of all the nuclei, and calculating the interaction energy as the difference between the electronic energy of the AB complex and the sum of the electronic energies, E_A° and E_B°, of the isolated entities A and B, a result to which appropriate corrections must be applied (*vide infra*).

The molecular orbitals for the supermolecule and for its components are obtained as canonical solutions of the LCAO–SCF equations expressed in terms of Gaussian basis sets selected as described in what follows. The correlation is introduced through Möller–Plesset theory at the MP2 level[18]. All computations have been performed using Gaussian-94[19] on the Cray computer at IDRIS.* Geometry optimizations were carried out at both the SCF and MP2 levels for all the individual molecules. For the complexes, we optimized only the relative disposition of the two interacting entities; the latter have been kept in their individual optimal geometries after having observed, in the case TMA–benzene, that only minute modifications in the individual bond length and angles occurred upon complexation, with a negligible effect on the values of the binding energies.

GAUSSIAN BASIS SETS

The basis set utilized is of fundamental importance if any accuracy is desired in supermolecule computations. Because the Gaussian program has its maximal efficiency when s and p Gaussian orbitals have the same exponents, we have adopted *as a starting point* the standard double-zeta 6-31G basis for carbon and nitrogen. For the nitrogen of the TMA ion, which carries a formal positive charge, it was deemed necessary to appropriately scale the 6-31G basis of the neutral nitrogen by applying to the most diffuse s and p Gaussians a scale factor obtained by energy optimization of

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NH_4^+ and $N(CH_3)_4^+$ ions. The same factor, $f = 1.09$, obtained for the two ions, reflects the contraction of the orbitals under the effect of positive charge.

For hydrogen, we have replaced the usual basis by the Huzinaga basis set with four components[20] contracted 3-1 for consistency. Throughout this study, the notation ''6-31G'' will designate the standard 6-31G basis modified as indicated above for N^+ and H.

To obtain viable values of molecular energies, it is necessary to augment the starting basis set with polarization orbitals. The standard choice uses ''valence polarization functions''[21] with an azimuthal quantum number l superior to that of the ordinary valence functions; that is, d for C, N, and N^+, and p for H. The exponents of the functions to add to our unpolarized basis were obtained by optimizing the molecular total energies at the SCF level, yielding $\alpha_d = 0.83$ for C, $\alpha_d = 0.91$ for N^+, and $\alpha_p = 1.22$ for H. The unpolarized basis augmented with the corresponding polarization orbitals is designated as 6-31G^{00}. This basis will be used essentially for a comparison with a better one, 6-31G$^{\alpha\alpha}$, in which we use another kind of polarization function (called Coulomb polarization functions by Mulliken[21]) defined as a series of s, p, and d ''semidiffuse'' orbitals appearing as a response of the valence orbitals to an internal or external electric field. Their exponents on each atom are determined in a stepwise fashion so as to obtain the optimal electric polarizability for the molecule considered with the basis set utilized,[22] a procedure justified by the Hylleraas variation principle.

This procedure was applied for the determination of the exponents of the s, p, and d orbitals, which, when added to the 6-31G basis previously defined, led to the maximal values of the molecular polarizabilities for CH_4, NH_3, NH_4^+, $N(CH_3)_4^+$, C_6H_6, and C_6H_5N. The final values adopted are given in Table I.

Due to the size of the molecules considered, the stepwise optimization process is rather lengthy; however, it appears justified by the quality of the polarizabilities obtained. Table II illustrates the situation with two molecules of our series, benzene and pyridine. The comparison with the polarizabilities obtained with the 6-31G^{00} basis using the energy-optimized polarization functions is rather striking. In view of the connection between the molecular polarizabilities and the London dispersion forces,[26] which are an important part of the second-order perturbation energy,[27] it is expected that the optimization procedure is appropriate for our purpose.

CORRECTIONS TO BINDING ENERGIES

Due to the incompleteness of the LCAO expansions,[28] the calculation of an interaction energy as the difference between the energy of the supermolecule, E_{AB}, and the sum of the energies of its fragments isolated, $E_A^\circ + E_B^\circ$, contains a built-in error, the basis set extension error (BSSE). The standard and simplest way to correct for the BSEE is to calculate the energy of each fragment A (or B) with its own basis set augmented by the basis set of B (or A), located at the points occupied, in the complex, by the nuclei of B (or A), and to subtract from the binding energy the so-called counterpoise correction:

$$E_A^\circ - E_A' + E_B^\circ - E_B'$$

Because we have kept the geometries of the ligands in the complexes unchanged with respect

TABLE I.
Exponents of Polarization Functions.

	C	N	N^+	H
Maximizing the polarizabilities (6-31G$^{\alpha\alpha}$)				
s, p	0.045	0.040	0.040	0.12
d	0.30	0.35	0.38	—
Optimizing the energies (6-31G^{00})				
p	—	—	—	1.22
d	0.83	0.83	0.91	—

TABLE II.
Experimental and Computed Molecular Polarizabilities for Benzene and Pyridine (Atomic Units).

	Benzene			Pyridine		
Polarizability	(a)	(b)	(c)	(a)	(b)	(c)
Experimental						
Ref. 23	79.2	79.2	44.1			
Ref. 24	83.1	83.1	42.8	80.2	73.1	39.0
Ref. 25				76.9	70.2	37.1
Computed						
Basis 6-31G$^{\alpha\alpha}$	82.7	82.7	45.7	77.5	73.9	41.1
	(78.9)	(78.9)	(44.3)	(74.6)	(69.3)	(39.7)
Basis 6-31G^{00}	68.5	68.5	20.8	64.3	58.6	18.2

(a), (b): In-plane components; (c): out-of-plane component; theoretical values are computed at the SCF level at optimal MP2 geometries (see text). Values in parentheses are computed at the SCF optimal geometries.

to those optimized individually, no further correction for geometry modifications[29] needs to be applied.

The second correction to the computed binding energy is the difference between the zero-point vibration energy (ZPVE) of the supermolecule and the sum of those of its fragments—quantities that can be obtained by the half-sum of the normal vibration frequencies. Because the complex comprises six more modes of vibration than the two fragments, the ZPVE correction comes as a *reduction*. In practice, due to the length of the calculation of the frequencies for the large entities considered, particularly at the MP2 level, we have computed the SCF 6-31G frequencies and scaled them by the uniform scaling factor of 0.9, according to the suggestion of Ref. 30. The corrections obtained are given in Table III for the four complexes considered.

Results and Discussion

The essential energy results for the four complexes computed at the SCF and MP2 levels with the unpolarized basis set and for the two polarized ones are given in Table IV. They concern, in each case, the most favorable complex obtained by optimization of the position of the ligand with respect to the most stable conformation of TMA (Fig. 2), in which the four methyl groups are disposed in such a way that each N^+C bond of one group is trans with respect to one hydrogen of the three other groups (e.g., H_{10}, H_{13}, and H_{15} on C_3, C_5, and C_4, respectively, are trans to N^+C_1).

TABLE III.
ZPVE Corrections (Kilocalories per Mole) Computed for Four Ligands in Their Most Favorable Complex with TMA.

Benzene	Pyrrole	Pyridine	Imidazole
0.52	0.60	0.68	0.79

Another totally symmetrical conformation of TMA (TMA II; Fig. 2b), obtained by rotating each methyl group 60° around its NC axis, was equally considered, but was found less stable than TMA I in all computations. The intrinsic stability of TMA I results in a greater stability of its best complex with benzene (see Table V) and also in better interaction energy, although conformer II allows a closer approach of the benzene molecule. Apart from this exploration we have considered only complexes with TMA I.

The disposition of the ligands in their most favorable complexes (basis 6-31G$^{\alpha\alpha}$) are given in Figure 3a for benzene–TMA I and in Figure 3b for benzene–TMA II; in Figure 4 for positions of secondary binding of benzene to TMA I, in Figures 5 and 6 for the best complexes of pyrrole, pyridine, and imidazole to TMA I. Table VI gives the distance to N^+ and the binding energies in the different complexes of benzene.

Examination of Table IV indicates that the binding energies appear distinctly in the order:

$$\text{benzene} < \text{pyrrole} < \text{pyridine} < \text{imidazole}$$

at all levels and for the three basis sets. Insofar as numerical values are concerned, both the correlation (MP2) effect and the BSSE correction are appreciable with larger effects occurring for the 6-31G$^{\alpha\alpha}$ basis, the richest one in polarization functions. Note that the term ''correlation'' in the last

TABLE IV.

Energy Characteristics (Kilocalories per Mole) of the Most Favorable Complexes with TMA I of Benzene, Pyrrole, Pyridine, and Imidazole Computed at SCF and MP2 Levels with Three Basis Sets.

		SCF			MP2				
Basis	Ligands	(a)	(b)	(c)	(d)	(e)	(f)	(g)	(h)
6-31G	Benzene	6.29	0.93	5.36	9.49	2.39	7.10	3.20	1.74
	Pyrrole	7.86	1.01	6.85	11.43	2.53	8.90	3.57	2.05
	Pyridine	12.81	1.05	11.76	16.81	3.29	13.52	4.00	1.76
	Imidazole	16.51	1.20	15.31	20.36	3.45	16.91	3.85	1.60
6-31G^{00}	Benzene	6.64	1.05	5.59	10.88	2.78	8.10	4.24	2.51
	Pyrrole	8.24	1.12	7.12	12.88	3.21	9.67	4.64	2.55
	Pyridine	11.49	1.01	10.48	16.09	2.95	13.14	4.60	2.66
	Imidazole	15.10	1.12	13.98	19.59	3.06	16.53	4.49	2.55
6-31G$^{\alpha\alpha}$	Benzene I[a]	6.02	0.86	5.17	15.85	6.73	9.12	9.82	3.95
	Benzene II[b]	5.31	0.78	4.53	14.85	6.64	8.20	9.54	3.66
	Pyrrole	7.58	1.13	6.45	17.47	6.76	10.71	9.89	4.26
	Pyridine	10.36	0.76	9.60	18.22	4.94	13.28	7.86	3.68
	Imidazole	13.69	0.87	12.82	21.12	4.85	16.27	7.43	3.45

(a): Binding energy; (b): basis set superposition error (BSSE); (c) binding energy corrected for BSSE, SCF level.(d), (e), (f): Same definitions for MP2 as (a), (b), and (c) for SCF. (g) = (d) − (a) =''Apparent'' correlation energy, without BSSE. (h) = (f) − (c) =''corrected'' correlation energy, after BSSE correction.

[a] Complex with TMA I.

[b] Complex with TMA II (see text).

column, being the difference MP2 − SCF, contains both the effect due to the reoptimization of the geometry and the proper correlation at the MP2 level. Due to the size of the systems, we could not go beyond the second order in Möller–Plesset theory. Other computations on more manageable systems (e.g., refs. 31 and 32) indicate that third- and fourth-order effects on the interaction energies are small. For the best basis set this correlation effect reaches 44% and 40% of the

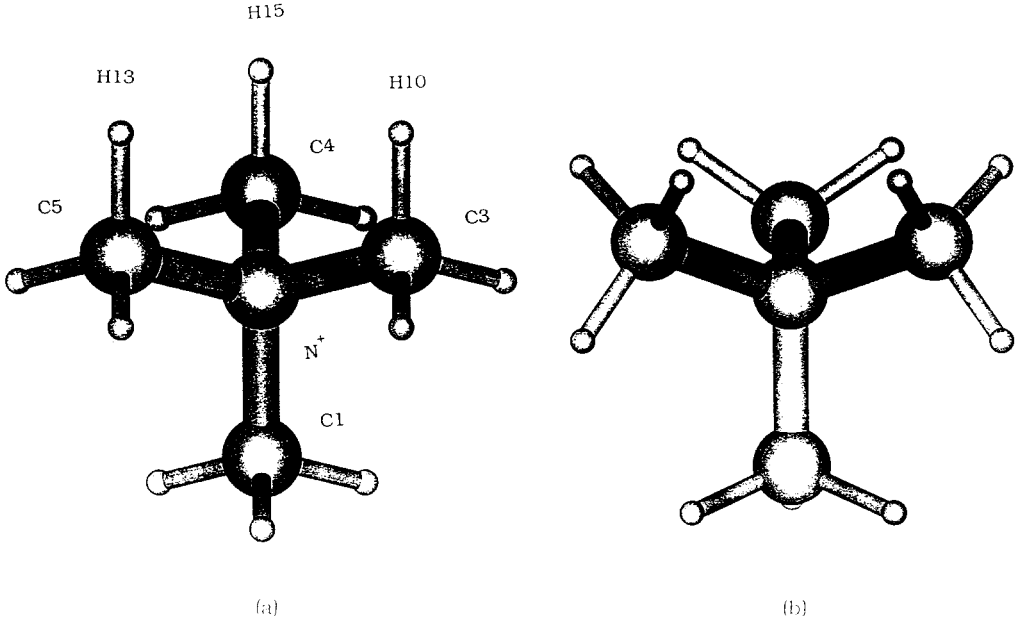


FIGURE 2. (a) TMA I; (b) TMA II (see text).

TABLE V.
Energies (a.u.), (6-31G$^{\alpha\alpha}$ basis) of TMA I and TMA II Conformers and of Their Most Favorable Complexes[a] with Benzene.

Conformer	SCF	MP2
TMA I[b]	−212.644 048	−213.307 682
TMA II[c]	−212.603 809	−213.267 467
TMA I−benzene	−443.318 483	−414.714 138
TMA II−benzene	−443.277 098	−444.672 329

[a] Not including the BSSE correction (see text).
[b] Optimized lengths (angstroms) and angles (degrees) are: SCF: CN = 1.505, CH = 1.086, HCN = 109.02; MP2: CN = 1.520, CH = 1.104, HCN = 108.63.
[c] Optimized lengths (angstroms) and angles (degrees) are: SCF: CN = 1.541, CH = 1.082, HCN = 109.99; MP2: CN = 1.560, CH = 1.100, HCN = 109.62.

binding energy for benzene and pyrrole, respectively, and 28% and 21% for pyridine and imidazole, respectively. Appreciably smaller percentages are obtained with the 6-31G^{00} basis.

Our best binding energy value for benzene (9.12 kcal/mol) compares very favorably with the enthalpy binding value of 9.4 kcal/mol deduced from gas-phase measurements,[1] an agreement which lends credence to the validity of the calculations with our 6-31G$^{\alpha\alpha}$ basis set. Neither the unpolarized basis, nor that augmented by valence polarization orbitals, could approach this level of accuracy. We shall thus compare the properties found for the four ligands by use of the 6-31G$^{\alpha\alpha}$ basis. However, note that, interestingly, aside from the differences observed in the energy values and in the approach distances, the relative dispositions (*vide infra*) found for the best complexes are very similar in the three bases.

BENZENE–TMA

Owing to the importance attributed to benzene as a model of cation−π interactions, and the fact that we have extended our study beyond the search for the best complex of this particular system, let us first comment on this ligand. As shown in Figure 4, its most favorable complex places it in a plane perpendicular to the C_1N^+ axis of TMA I with its center at 4.16 Å of the quaternary nitrogen (Table VI). Due to the pyramidal structure of the ion and of the methyl carbons, the plane of benzene is essentially parallel to the plane of three hydrogens, one for each methyl group. The most stable orientation of benzene about the axis is that of Figure 3a, but its rotation in the plane is easy (an energy loss of 0.067 and 0.073 kcal/mol for rotations of 15° and 30°, respectively, was computed at the SCF level). No stable position of the molecule with respect to TMA was found in trying to orient its axis vertically toward the N^+ atom inside the solid angle made by three N−methyl bonds.

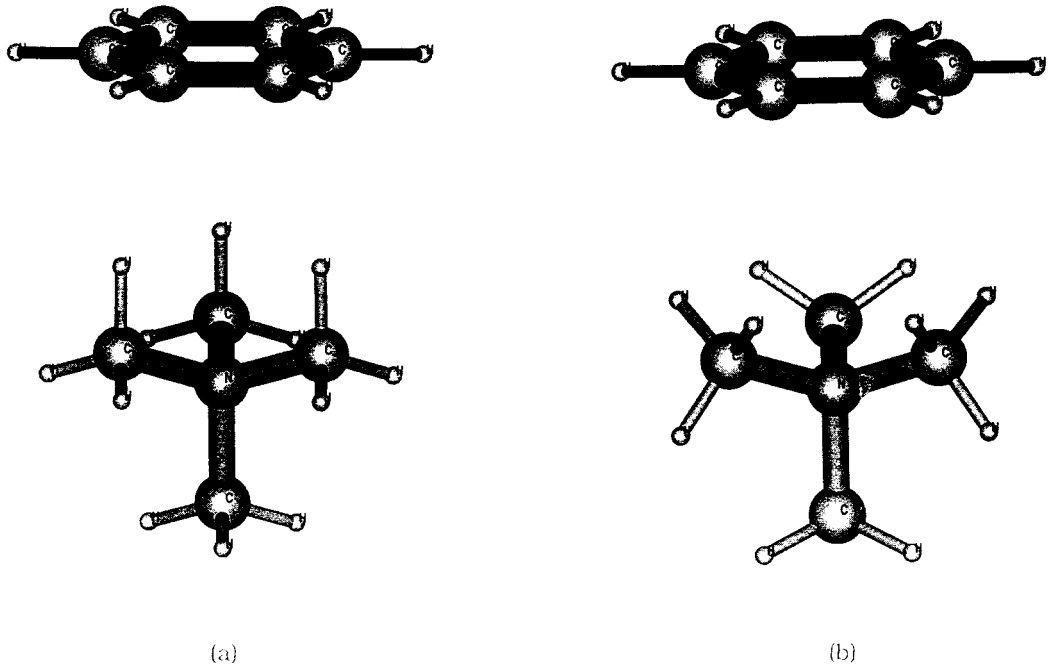
It may be noted that, in the best complex, the three positively charged hydrogens of the three methyl groups [q_H(MP2) = +0.43] are disposed in the best fashion with respect to the carbon atoms of benzene so as to favor global charge−charge interaction [q_C(MP2) = −0.30] and best overlap with their π orbitals. Note that, owing to the symmetry of TMA, equivalent complexes exist with benzene perpendicular to the three other CN^+ directions.

A similar disposition (Fig. 3b) was found for the best complex of benzene with TMA II where the binding energy is smaller (8.2 kcal/mol at the MP2 level). The benzene molecule is centered on the C_1N^+ axis, a little closer (3.96 Å) to N^+ than in TMA I. In that case, the plane of benzene is essentially parallel to the plane of six hydrogens (two for each methyl group): the disposition of the carbon atoms of benzene with respect to the hydrogens is less favorable, but there are a total of six and the attraction toward N^+ is less hindered, resulting in a closer approach.

TABLE VI.
Positions and Binding Energies (without BSSE) of Benzene Around TMA in Different Sites (see text).

	Site Facing:							
	3 methyls (3 hydrogens)		3 methyls (6 hydrogens)		2 methyls (4 hydrogens)		1 methyl (3 hydrogens)	
	SCF	MP2	SCF	MP2	SCF	MP2	SCF	MP2
d	4.61	4.16	4.58	3.96	4.85	4.33	5.20	—
BE	6.02	15.85	5.31	14.85	5.04	12.94	4.74	—

d (angstroms): Distance to N^+; BE (kilocalories per mole): binding energy.



(a) (b)

FIGURE 3. (a) The best complex, benzene–TMA I; (b) the best complex, benzene–TMA II.

These observations concerning the role of the methyl groups led us to investigate the possibilities of binding by directly approaching one methyl group along its N^+C axis, with the benzene plane parallel to the plane of its three hydrogens. The computations, done for TMA I, indicate that there exists a secondary minimum of this sort, less favorable in energy and more distant from N^+ than the best adduct (see Table VI and Fig. 4a). Finally, we also considered an approach toward *two* methyl groups, along the bissectrix of the CNC angle, which indicated the existence of another secondary binding site of benzene with an intermediate energy, in a plane parallel to that of four methyl hydrogens at an intermediate distance from N^+ (Fig. 4b). Again, due to the symmetry, there are four equivalent binding possibilities to a single methyl and four others facing two methyl groups.

These data concerning benzene indicate not only the fact that TMA can form an appreciably stable complex with the benzene molecule and that this binding can occur in four directions around the ion, but also that a number of secondary sites are available on the periphery with a non-negligible interaction energy, making the structure of TMA a particularly well-adapted binder of phenyl rings: its known capacity to act as an inhibitor of the enzyme acetylcholine esterase[33] may be due to its ability to occupy the phenyl aromatic sites along the path of the substrate.

An accessory remark may be made concerning the distances of approach given in Table VI: that is, they all show a shortening at the MP2 level with respect to the SCF level. This was a general feature found for all compounds in the present computations and for both polarized basis sets.

In connection with the positions of favorable binding found for benzene by calculation, it is of interest to mention a recent study[34] of the stereochemistry of the interaction between a phenyl ring and an $RN^+(CH_3)_3$ group in proteins, based on the statistics of 154 crystal structures from the Cambridge Structural Database.[35] This analysis indicates a clustering of phenyl rings centered between methyl groups at about 4.5 Å from the nitrogen atom of the onium ion, and tangent to a sphere centered on the nitrogen, a position corresponding closely to that of the most stable complex of TMA found in our study. On the other hand, the statistics indicated a secondary maximum in the radial distribution function, with the phenyl group centered on the axis of one methyl group at about 6 Å from the nitrogen with a tilt of the ligand toward the other methyls, away from

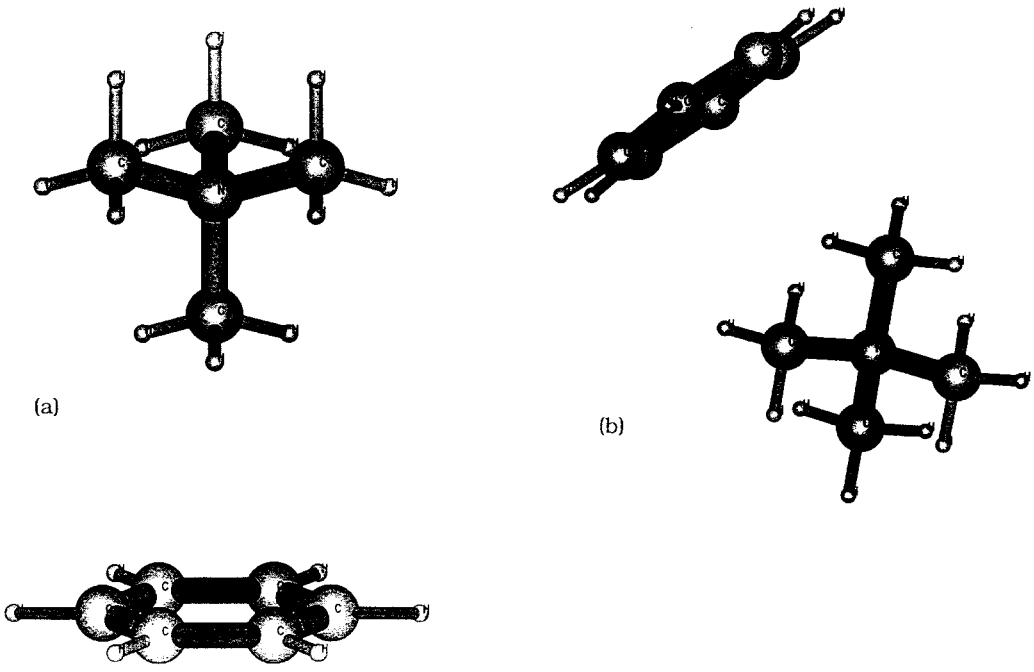


FIGURE 4. Secondary complexes of benzene on TMA I: (a) facing one methyl group; (b) facing two methyl groups.

the substituent *R*. This position could be related to the secondary binding possibilities revealed by our calculations on TMA, but it is not possible to give a closer correlation without explicit theoretical calculations of the effect of substituent *R* on binding. This is likely to affect more the secondary sites than the position involving three methyl groups.

PYRROLE–TMA

The approach of pyrrole to TMA I leads to a system a little more favorable in energy than the most favorable complex of benzene (10.7 vs. 9.1 kcal/mol at the 6-31G$^{\alpha\alpha}$ MP2 level). Like benzene, the planar ligand faces the plane of three methyl hydrogens, in a plane slightly closer to TMA I than that of benzene and very slightly inclined toward the ion; the ''center'' of the molecule being displaced with respect to the TMA axis; the orientation is shown in Figure 5. Due to the symmetry of the ion, an equivalent binding site exists with a symmetrical disposition of the nitrogen of pyrrole with respect to the $C_1N^+H_{15}$ plane and two equivalent pairs of sites are disposed similarly with respect to the $C_1N^+H_{10}$ plane and also with respect to $C_1N^+H_{13}$, a similar situation being additionally encountered around each triad of methyl groups.

It is to be noted that the best positions of pyrrole obtained at the SCF level with the 6-31G$^{\alpha\alpha}$ basis, and also with the two other basis sets at the SCF and MP2 levels, are essentially similar to that just described, with some differences in the inclination of the plane of the molecule and in the rotation of the nitrogen atom in the plane.

Overall, it can be said at this point that the complexes of benzene and pyrrole belong to the same category both in energy and in general orientation of the ligands with respect to TMA, namely in a plane, or nearly so, parallel to the plane of the three highest hydrogens of TMA (Fig. 2a). The situation appears quite different for the other two compounds.

PYRIDINE–TMA AND IMIDAZOLE–TMA

We have already mentioned the fact that the binding energies of pyridine and imidazole are appreciably larger than those of benzene and pyrrole, a distinction already essentially present at all levels of calculation (Table IV). A concomitant characteristic of the two compounds is that they both prefer an orientation nearly perpendicular to the plane of the three highest hydrogens of TMA, with their pyridine-like nitrogen pointing toward N^+ in the interior of the triad of methyl groups (Fig. 6). For both molecules, this nitrogen is nearly on the symmetry axis of TMA, which itself nearly

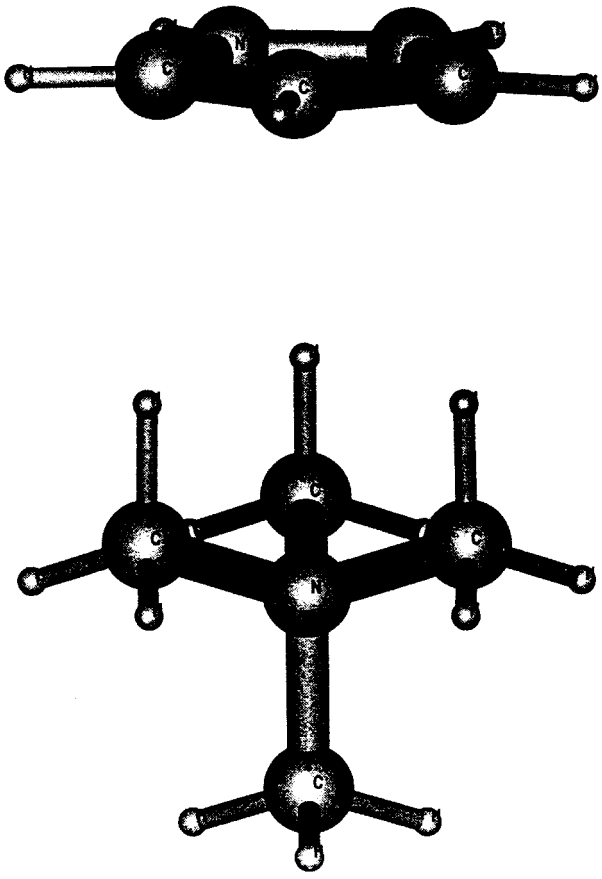


FIGURE 5. The best complex pyrrole–TMA I.

coincides with the symmetry axis of pyridine and with the NN axis of imidazole. Again, very similar dispositions were found with the other basis sets, and at the SCF and MP2 levels. No equilibrium position perpendicular or nearly perpendicular to the TMA axis could be found for these two nitrogen compounds, even when using such a position as starting point for the optimization; clearly, the N^+N Coulomb attraction tips the balance in favor of the vertical position. Although both heterocycles are also systems of six π electrons, the cation–π interaction is not the dominant feature here as it is for benzene and pyrrole; in pyridine and imidazole, the in-plane nitrogen lone pair tends to orient the molecule so as to insure maximum attraction toward the positive nitrogen of TMA and clearly wins over the cation–π interaction. The structure of the adduct is then reminiscent of the situation in the TMA–H_2O complex, where the oxygen of the water molecules inserts itself in the angle of the three methyl groups.[1] Note that the binding energies of pyridine and imidazole follow the same increasing order as their dipole moments—2.4 Debye units computed for pyridine and 3.9 for imidazole—another indication of the dominance of the ion–dipole interaction.

Conclusion

This theoretical comparative study of the complexation of the tetramethyl ammonium ion with benzene and three related heterocycles containing six π electrons has provided evidence of the interesting differences in behavior. Whereas benzene and pyrrole form complexes of a similar nature (similar binding energies and similar disposition of the ligand perpendicular to the TMA axis, nearly so for pyrrole), indicating an analogous dominance of the ''cation–π'' interaction in the two systems, the more polar molecules, pyridine and imidazole, interact more strongly with the ion and adopt an orientation perpendicular to that adopted by benzene and pyrrole so as to maximize the ion–dipole interaction. These results indicate that caution must be exercised in generalizing the notion of onium ion–aromatic interaction from one system to another, even if they contain the same number of π electrons.

Concerning the problem of the interaction of onium ions/aromatic amino acids in biology and pharmacology, it appears that TMA, by its numerous potential sites for binding, offers many possibilities for favorable interaction with phenyl groups in agreement with the fact that both phenylalanines and tyrosines are observed in the neighborhood of the ammonium head of choline derivatives in different crystal structures.[5,7,9–12] Furthermore, the binding properties found for benzene and pyrrole in nearly the same plane allow inference that indole, where the two entities are condensed, should bind in a similar fashion in a cation–π-dominated interaction in agreement with the observation of tryptophan amino acids near choline heads in the X-ray structures mentioned. On the other hand, the different binding properties found for imidazole is in keeping with the fact that unprotonated histidines do not appear close to the onium heads in these structures, where they have a different role.

Recently, a molecular orbital study of complexes between the Na^+ ion and a number of aromatics, designed for modeling cation–π interactions has been presented.[37] Unlike our findings, in the case of TMA, the brute SCF interaction energies obtained at the 6-31G** level without the

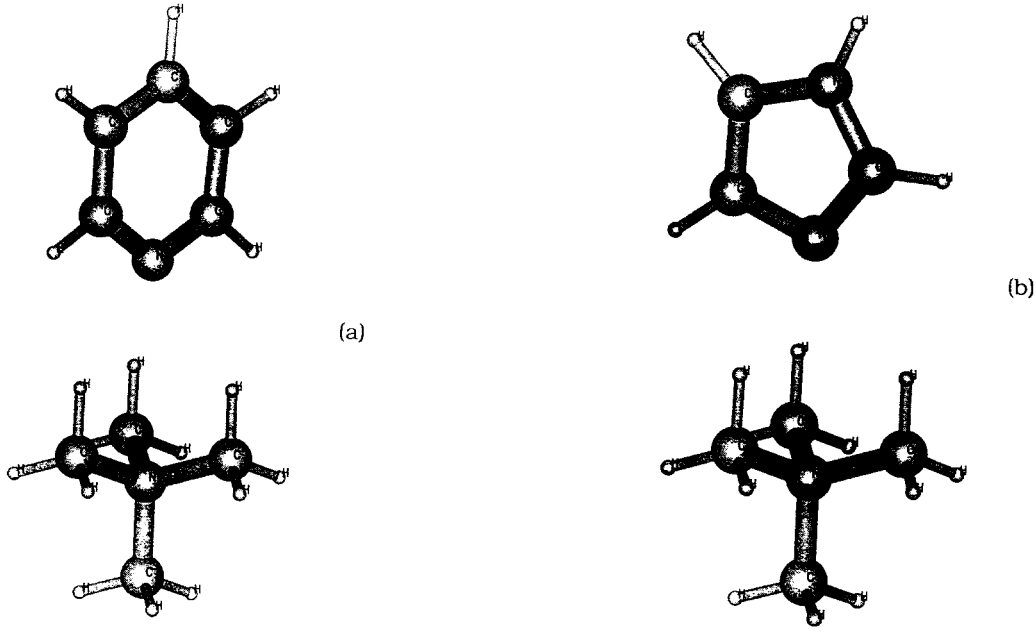


FIGURE 6. The best complexes: (a) pyridine–TMA I; (b) imidazole–TMA I.

MP2 correlation contribution and significant BSSE correction are consistent with experiment in the case of Na^+–benzene binding. Clearly, the smaller magnitude of our corresponding value computed for TMA can be attributed to the fact that a charged bare atom, like Na^+, can hardly simulate a substituted quarternary ammonium ion in which the cation–π interaction is mediated by CH bonds, a difference particularly visible by the appreciably larger equilibrium distance in the TMA complex and also by the fact that the correlation correction and the BSSE are appreciably larger for TMA than for Na^+. Despite these differences, the ordering of the binding energies with Na^+ appears consistent with our BSSE-corrected MP2 values, provided, however, that the interactions of pyridine and imidazole taken in Ref. 37 are those of true minima rather than those corresponding to the ion interacting with the π system only. As far as predicting absolute values, and even ordering in some cases, extrapolation from one cation to another must clearly be done with caution.

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